

under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

*Amendments*

*In the Specification:*

At page 22, lines 1-2, please change the heading to the following:

B<sup>1</sup>

**Example 6. Activity of WGA-LH<sub>N</sub>/A in primary neuronal cultures**

At page 22, lines 23-24, please change the heading to the following:

B<sup>2</sup>

**Example 7. Activity of ExL-LH<sub>N</sub>/A in an electrophysiological model of pain**

At page 23, lines 12-13, please change the heading to the following:

B<sup>3</sup>

**Example 8. Activity of ExL-LH<sub>N</sub>/A in behavioural models of pain**

*In the Claims:*

Please cancel claim 17 without prejudice or disclaimer.

Please substitute the following claims 1-13, 15, 16, 18-34, 36-43, 46-49, 51, 52  
and 54 for the pending claims 1-13, 15, 16, 18-34, 36-43, 46-49, 51, 52 and 54:

- Sub C1*
- B4*
1. (Once amended) ~~An agent, for the treatment of pain, that comprises:- a galactose-binding lectin; a light (L) chain or an L-chain fragment of a clostridial neurotoxin, which L-chain or L-chain fragment includes the active proteolytic enzyme domain of the L-chain; and a molecule or domain with membrane translocating activity; wherein the galactose-binding lectin, L-chain or fragment, and molecule or domain with membrane translocating activity are linked together.~~
  2. (Once amended) ~~An agent according to Claim 1 in which the membrane translocation domain is a heavy (H) chain of a clostridial toxin.~~
  3. (Once amended) ~~An agent according to Claim 1 in which the membrane translocation domain is selected from the group consisting a translocation domain of diphtheria toxin, a translocation domain of pseudomonas exotoxin, a translocation domain of anthrax toxin, and a translocating fusogenic peptide.~~
  4. (Twice amended) An agent according to Claim 1 in which the lectin binds to an oligosaccharide that contains an exposed  $\beta$ -D-galactosyl residue.
  5. (Twice amended) An agent according to Claim 1 in which the lectin binds to an oligosaccharide that contains an exposed  $\alpha$ -D-galactosyl residue.

6. (Twice amended) An agent according to Claim 1 in which the lectin binds to an oligosaccharide that contains an exposed N-acetylgalactosamine residue.
7. (Twice amended) An agent according to Claim 1 in which the lectin has been obtained from a species of plant.
8. (Twice amended) An agent according to Claim 1 in which the lectin has been obtained from a species of the genus *Erythrina*.
9. (Once amended) An agent according to Claim 8 in which the lectin has been obtained from *E. cristagalli*.
10. (Once amended) An agent according to Claim 8 in which the lectin has been obtained from *E. corallodendron*.
11. (Twice amended) An agent according to Claim 7 in which the lectin has been obtained from *Glycine max*.
12. (Twice amended) An agent according to Claim 7 in which the lectin has been obtained from *Arachis hypogaea*.
13. (Twice amended) An agent according to Claim 7 in which the lectin has been obtained from *Bandeirea simplicifolia*.
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B4  
cont

B<sup>5</sup>

15. (Twice amended) An agent according to Claim 1 in which the lectin is of bacterial origin.

16. (Once amended) An agent according to Claim 15 in which the lectin has been obtained from *Pseudomonas aeruginosa*.

18. (Twice amended) An agent according to Claim 1 in which the lectin has been contacted with an enzyme, and retains an ability to bind to an oligosaccharide structure having an exposed galactose or N-acetylgalactosamine residue.

B<sup>6</sup>

19. (Twice amended) An agent according to Claim 1 in which the lectin has been contacted with a chemical, and retains an ability to bind to an oligosaccharide structure having an exposed galactose or N-acetylgalactosamine residue.

Sub C<sup>2</sup>

20. (Twice amended) An agent according to Claim 2, wherein the H<sub>C</sub> domain of the H-chain has been removed or modified to remove or reduce the native binding affinity of the H-chain for motor neurons.

21. (Twice amended) An agent according to Claim 20, wherein the H-chain has been contacted with a derivatising chemical to reduce or remove the native binding affinity of the H-chain for motor neurons.

22. (Twice amended) An agent according to Claim 20, wherein the H-chain has been mutated by the inclusion of at least one amino acid deletion, insertion, and/or substitution to reduce or remove the native binding affinity of the H-chain for motor neurons.
23. (Twice amended) An agent according to Claim 20, wherein the H-chain has been contacted with a proteolytic agent to reduce or remove the native binding affinity of the H-chain for motor neurons.
24. (Once amended) An agent according to Claim 20 in which the H<sub>C</sub> domain has been completely removed leaving the H<sub>N</sub>-fragment of a clostridial neurotoxin.
25. (Twice amended) An agent according to Claim 1 in which the L-chain of the clostridial neurotoxin is a botulinum neurotoxin L-chain.
26. (Twice amended) An agent according to Claim 25 in which the L-chain of the clostridial neurotoxin is a botulinum neurotoxin type A L-chain.
27. (Twice amended) An agent according to Claim 25 in which the L-chain of the clostridial neurotoxin is a botulinum neurotoxin type B L-chain.

B4  
cont

28. (Twice amended) An agent according to Claim 1 which has been formed by the coupling of a galactose-binding lectin to the LH<sub>N</sub> fragment of botulinum neurotoxin type A.

29. (Once amended) An agent according to Claim 28 which has been formed by the coupling of the galactose-binding lectin from *Erythrina cristagalli* to the LH<sub>N</sub> fragment of botulinum neurotoxin type A.

30. (Once amended) An agent according to Claim 28 which has been formed by the coupling of the galactose-binding lectin from *Erythrina corallodendron* to the LH<sub>N</sub> fragment of botulinum neurotoxin type A.

B6  
cont

31. (Once amended) An agent according to Claim 28 which has been formed by the coupling of the galactose-binding lectin from *Glycine max* to the LH<sub>N</sub> fragment of botulinum neurotoxin type A.

Sub C3

32. (Twice amended) An agent according to Claim 2 in which the H-chain has been obtained from a different clostridial neurotoxin than that from which the L-chain or fragment thereof has been obtained.

33. (Once amended) An agent according to Claim 32 in which the H-chain has been obtained from botulinum neurotoxin type A and the L-chain or fragment thereof from botulinum neurotoxin type B.

B<sup>6</sup>  
cont

34. (Once amended) An agent according to Claim 32 in which the H-chain has been obtained from botulinum neurotoxin type A and the L-chain or fragment thereof from tetanus neurotoxin.

36. (Twice amended) An agent according to Claim 2 in which the L-chain or L-chain fragment is linked to the H-chain by a direct covalent linkage.

37. (Twice amended) An agent according to Claim 2 in which the L-chain or L-chain fragment is linked to the H-chain by a covalent linkage which includes at least one spacer region.

38. (Twice amended) An agent according to Claim 1 in which the L-chain or fragment is a polypeptide produced by recombinant technology.

B<sup>7</sup>  
sub C4

39. (Twice amended) An agent according to Claim 1 in which the lectin is linked to the L-chain or fragment thereof, and/or to the molecule or domain with membrane translocating activity by a direct covalent linkage.

40. (Twice amended) An agent according to Claim 1 in which the lectin is linked to the L-chain or fragment thereof, and/or to the molecule or domain with membrane translocating activity by a covalent linkage which includes at least one spacer region.

41. (Twice amended) An agent according to Claim 1 in which the lectin, L-chain or fragment thereof, and molecule or domain with membrane translocating activity are produced as a recombinant fusion protein.

42. (Twice amended) An agent according to Claim 1 in which the lectin protein has at least one amino acid insertion, deletion, or substitution when compared with the polypeptide sequence of the corresponding native lectin protein, and retains an ability to bind to an oligosaccharide structure having an exposed galactose or N-acetyl galactosamine residue.

43. (Once amended) An agent according to Claim 42 in which the nucleic acid coding for the lectin protein has at least one nucleotide deletion, insertion and/or substitution when compared with the nucleic acid sequence coding for the corresponding native lectin protein.

46. (Twice amended) A method for obtaining an agent according to Claim 1 which comprises:- the covalent attachment of a galactose-binding lectin, an L-chain or an L-chain fragment of a clostridial neurotoxin which L-chain or an L-chain fragment includes the active proteolytic domain of the L-chain, and a molecule or domain with membrane translocating activity; thereby providing an agent in which the galactose-binding lectin, L-chain or L-chain fragment, and molecule or domain with membrane translocating activity are linked together.



47. (Twice amended) A method for obtaining an agent according to Claim 46 wherein the covalent attachment includes at least one spacer region.

48. (Twice amended) A method according to Claim 46 in which the membrane translocation domain is the heavy chain of a clostridial toxin.

49. (Twice amended) A method according to Claim 46 in which the membrane translocation domain is selected from the group consisting a translocation domain of diphtheria toxin, a translocation domain of pseudomonas exotoxin, a translocation domain of anthrax toxin, and a translocating fusogenic peptide.

51. (Twice amended) A method of controlling the transmission of sensory information from a primary sensory afferent to a projection neuron by administering an effective amount of the agent of Claim 1.

52. (Twice amended) A method of controlling the transmission of sensory information from a primary nociceptive afferent to a projection neuron by administering an effective amount of the agent of Claim 1.

54. (Twice amended) A method of controlling the sensation of pain by administering an effective amount of the agent of Claim 1.

Please add the following new claims 58-62:

58. (New) A method according to Claim 51, wherein the route of administration is selected from the group consisting of intrathecal, subcutaneous, and epidural.

59. (New) A method according to Claim 52, wherein the route of administration is selected from the group consisting of intrathecal, subcutaneous, and epidural.

60. (New) A method according to Claim 53, wherein the route of administration is selected from the group consisting of intrathecal, subcutaneous, and epidural.

61. (New) A method according to Claim 54, wherein the route of administration is selected from the group consisting of intrathecal, subcutaneous, and epidural.

62. (New) A method according to Claim 57, wherein the route of administration is selected from the group consisting of intrathecal, subcutaneous, and epidural.

B 1'  
ADD  
D<sub>2</sub>